Complete Summary

GUIDELINE TITLE

Management of unresected stage III non-small cell lung cancer: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Okawara G, Mackay JA, Evans WK, Ung YC, Lung Cancer Disease Site Group. Management of unresected stage III non-small cell lung cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Jan. 50 p. [117 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Unresected, stage III non-small cell lung cancer (NSCLC)

Note: Unresected disease is defined as a tumor that, for either technical or medical reasons, cannot be completely resected or removed

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Internal Medicine
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To address the following questions:

- What is the role of different schedules or doses of radiotherapy as a treatment in patients with unresected stage III non-small cell lung cancer (NSCLC)?
- Does chemotherapy combined with radiotherapy improve survival compared with radiotherapy alone in patients with unresected stage III non-small cell lung cancer?
- Which sequence of radiotherapy combined with chemotherapy is most effective in improving survival for patients with unresected stage III non-small cell lung cancer?
- Which chemotherapy regimen(s), combined with radiotherapy, is most effective in improving survival for patients with unresected stage III non-small cell lung cancer?

TARGET POPULATION

Adult patients with unresected, clinical or pathological, stage III non-small cell lung cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Radiotherapy alone
    - Immediate versus delayed radiotherapy
    - Variable doses and schedules of conventional radiotherapy
    - Hyperfractionated radiotherapy (not recommended outside the context of a clinical trial)
2. Chemoradiation versus radiation alone
    - Chemotherapy as a radiosensitizer versus conventional radiotherapy alone
    - Chemoradiation versus conventional radiation alone
    - Chemoradiation versus hyperfractionated or accelerated radiation alone

3. Timing of radiotherapy relative to chemotherapy
4. Different chemotherapies within chemoradiation regimens

MAJOR OUTCOMES CONSIDERED

- Response rate
- Survival
- Symptom control
- Quality of life
- Toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature searches were conducted in MEDLINE (1966 through November 2005), EMBASE (1980 through 2005, week 46), the Cochrane Library (2005, Issue 4), and the Cochrane Central Register of Controlled Trials (2005, issue 4) using the following search terms as MEDLINE or EMBASE subject headings "carcinoma, non-small-cell lung", "lung carcinogenesis", "lung adenocarcinoma", "lung alveolus cell carcinoma", "lung, non small cell cancer", "lung squamous cell carcinoma", "radiotherapy" and "cancer radiotherapy", combined with the text words "non small cell lung", "radiotherapy", "radiation therapy", "chemoradiation", "inoperable", or "unresectable", and the following publication types and study designs: practice guidelines, systematic reviews or meta-analyses, randomized controlled trials, and controlled clinical trials.

In addition, conference proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO, 1999 through 2005) and the American Society for Therapeutic Radiology and Oncology (ASTRO, 1999 through 2004) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov) were searched for existing, evidence-based practice guidelines published since 2000.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from those sources were searched for additional trials as were the reference lists from relevant review articles.

Inclusion Criteria

Articles were included in this systematic review if they were fully published reports or abstract of meta-analyses or randomized trials (phase II or III) comparing the following in patients with unresectable stage III non-small cell lung cancer (NSCLC):

1. Different schedules or doses of radiotherapy as a single modality treatment
2. Radiotherapy alone versus the same radiotherapy regimen combined with chemotherapy
3. Different chemoradiation regimens that differ only in the radiation regimen used
4. Different chemoradiation regimens that differ only in the chemotherapy regimen used
5. Timing of radiotherapy and chemotherapy administration within a chemoradiation treatment approach

In addition, evidence-based practice guidelines or systematic reviews were eligible, which addressed radiotherapy-based treatment for unresectable stage III NSCLC and included recommendations published since 2000.

Exclusion Criteria

The following were not considered:

1. Trials evaluating any of the following treatment options or comparisons: older radiotherapy equipment (e.g., equipment that antedated Cobalt-60), 3D conformal radiotherapy, bronchial artery infusion chemotherapy, split-course radiotherapy when compared with another radiotherapy schedule, or conventional compared with altered fractionation radiotherapy (see *Related Guidelines* section of the original guideline document).
2. Trials of chemoradiation involving a non-platinum chemotherapy combination and published prior to 1995. Meta-analyses have shown a survival advantage for chemoradiation over radiation alone for platinum-based chemotherapy but not other chemotherapies.
3. Trials randomizing only patients that had responded to, or did not progress on, induction chemotherapy
4. Trials that did not report the required outcomes by treatment group. For trials with palliative intent, required outcomes included symptom control or quality of life (QOL); for other trials, survival data were required.
5. Letters and editorials reporting trial data
6. Papers published in a language other than English

NUMBER OF SOURCE DOCUMENTS

Forty-seven randomized trials and six meta-analyses met the eligibility criteria for this systematic review.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The Disease Site Group (DSG) decided not to statistically pool data from randomized controlled trials for the following reasons:

- There were no consistent radiotherapy dose/schedule comparisons among trials of palliative radiotherapy
- Several meta-analyses comparing chemoradiation with radiation alone have already been conducted although no consistent chemotherapy regimens or radiotherapy schedules or doses have been compared across trials
- Trials comparing the timing of chemoradiation administration have primarily been published in abstract form to date and provide limited data for statistical pooling

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This evidence-based series was developed by the Lung Disease Site Group (DSG) of Cancer Care Ontario (CCO's) Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on the management of unresected stage III non-small cell lung cancer (NSCLC) developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

This practice guideline was discussed at Lung DSG meetings in 2003 and 2004. Much of the discussion centred on those patients suitable for aggressive chemoradiotherapy. Although a full publication of the Radiation Therapy Oncology Group (RTOG) 9410 phase III study is not yet available, the most recent update of that trial was reported in abstract form at the 2003 American Society of Clinical Oncology (ASCO) meeting. The results showed a statistically significant survival advantage for concurrent over sequential chemoradiotherapy and were consistent with the data from two other trials, one published phase III trial and one published randomized phase II trial. The DSG members agreed that a recommendation for concurrent treatment should be made.

The role of induction or consolidation chemotherapy, in combination with concurrent chemoradiation, was discussed by the DSG, and the contrasting results of two trials were noted. One trial observed a trend towards a survival benefit for immediate concurrent chemoradiation followed by consolidation chemotherapy compared with induction chemotherapy followed by concurrent chemoradiation, and the other trial detected no statistical difference in survival for chemoradiation with or without induction chemotherapy. An informal poll of DSG members in 2003 indicated that most Ontario cancer centres have already adopted a treatment scheme of early concurrent chemoradiation without induction

chemotherapy; however, the group felt that the conflicting evidence did not allow a firm recommendation to be made regarding the use of induction or consolidation chemotherapy.

While most of the studies provided aggressive treatment to a patient population with good performance status (PS) (Eastern Cooperative Oncology Group [ECOG] 0-1) and limited weight loss (typically defined as <5% in the preceding three months), it was pointed out that some trials included patients with a weight loss of up to 10%. For those less fit patients, the DSG felt that it was reasonable to consider concurrent or sequential therapy, depending upon other patient factors and following, as always, a full discussion with the patient of the treatment options, goals of therapy, and potential adverse effects. For symptomatic patients with poor performance status or significant weight loss, standard radiation alone offers the potential for symptomatic relief. However, the DSG agreed that single-fraction radiation of 10 gray (Gy) should not be considered a standard approach given the decreased survival and quality of life (QOL) observed in comparison with a multifractionated regimen in one trial. The DSG emphasized the importance of adequate performance status assessment when evaluating treatment options.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External Review by Ontario Clinicians

Following review and discussion of sections 1 and 2 of the original guideline document, the Lung Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Practitioner feedback was obtained through a mailed survey of 121 practitioners in Ontario, including 22 radiation oncologists, 36 medical oncologists, 27 surgeons, 33 respirologists, one hematologist, one pathologist, and one practitioner from nuclear medicine. In addition, the guideline and practitioner survey was mailed out to 150 family physicians, randomly selected from a database of approximately 1000 members, to gauge their interest in the current guideline documents and to determine if they would like to participate in the practitioner feedback process in the future. The survey consisted of items evaluating the method, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written

comments were invited. The practitioner feedback survey was mailed out on July 14, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung DSG reviewed the results of the survey.

Practice Guidelines Coordinating Committee (PGCC) Approval Process

Following completion of the practitioner feedback process, the literature search was updated and the new evidence was consistent with the guideline recommendations. The revised guideline was circulated to 13 members of the PGCC for review and approval. Nine members of the Committee returned ballots. One member is a co-chair of the Lung DSG and was therefore not eligible to comment on the document. Six PGCC members approved the practice guideline report as written. One member requested clarification on whether a "wait and see" strategy for palliative radiation alone, as described in the *Choice of Topic and Rationale* section of the original guideline document, is a policy for any organization. In addition, one member commented that radiotherapy may be delayed at centres where radiation services are limited and concurrent chemoradiation may then be difficult to implement, and one member expected that fatigue, which is frequently associated with chemotherapy administration, would also be a common toxicity with chemoradiation.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- For patients with good performance status (Eastern Cooperative Oncology Group, 0-1) and minimal weight loss (usually defined as <5% in the preceding three months):
    - Chemoradiation improves survival compared with radiotherapy alone and concurrent chemoradiation is recommended, with cisplatin-based chemotherapy and thoracic radiation of at least 60 gray (Gy) in 30 fractions given over a six-week period.
    - Insufficient evidence exists to recommend a specific cisplatin-based regimen for use in a concurrent chemoradiation schedule. However, in the opinion of the Lung Cancer Disease Site Group, reasonable treatment options include cisplatin combined with one of etoposide, vinorelbine, or vinblastine.
- For symptomatic patients with poor performance status (Eastern Cooperative Oncology Group, >1) and significant weight loss (usually defined as >10% in the preceding three months):
    - Radiotherapy for symptom palliation is recommended.
    - Insufficient evidence exists to determine the optimal dose or timing of radiotherapy when the goal of therapy is symptom palliation. Reasonable treatment options include 20 Gy in five fractions and 17 Gy in two fractions given one week apart. Radiotherapy administered in a single fraction of 10 Gy is not recommended based on the decreased survival and quality of life observed when compared with multifractionated radiotherapy in one Canadian trial. However, in the opinion of the Lung Cancer Disease Site Group, single fractions of radiotherapy less than 10 Gy may be appropriate in some clinical circumstances.

    - Palliative chemotherapy for patients with stage III disease is not reviewed in this guideline. For guidelines on palliative chemotherapy for locally advanced (stage IIIB) or metastatic (stage IV) disease, please visit the Cancer Care Ontario Web site.
- For patients with borderline performance status or moderate weight loss (5-10%):
    - Concurrent or sequential chemoradiation is an option though the quality and quantity of evidence is not as compelling as that for patients with good performance status and minimal weight loss.
- Hyperfractionated radiation is not recommended outside the context of a clinical trial (see *Related Guidelines* section in the original guideline document).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Fifteen randomized trials examined various policies or dose and schedule combinations for radiotherapy administration. Among the fully published trials, no statistically significant survival differences were detected for immediate versus delayed administration of radiotherapy (one trial) or different doses of hyperfractionated radiotherapy (one trial). Of the 11 fully published trials that compared varying doses and schedules of standard fractionated radiotherapy, three detected a statistically significant survival advantage with higher multifractionated radiation doses (20 gray [Gy] in five fractions versus 10 Gy in one fraction, p=0.03; 39 Gy in 13 fractions versus 17 Gy in two fractions, p=0.03; 30 Gy in 10 fractions versus 16 Gy in two fractions, p=0.03). One trial detected a survival advantage for 16 Gy in two fractions compared with 20 Gy in five fractions (p=0.016); however, the reliability of this result is limited by the size of the trial (n=100) and the fact that survival was a secondary outcome.
- Six meta-analyses compared chemoradiation with radiation alone; three focused exclusively on trials that administered concurrent chemoradiation. There was considerable overlap in the studies included in each meta-analysis, and the results were consistent. The largest meta-analysis involved 22 studies and individual patient data from more than 3,000 patients. That meta-analysis detected a statistically significant overall survival benefit for the use of chemoradiation with a pooled hazard ratio of 0.90 (p=0.006) or a 10% relative reduction in the risk of death, which translated into an absolute benefit of 3% at two years and 2% at five years. The survival benefit

associated with chemoradiation was maintained in a subgroup analysis of 11 trials involving cisplatin-based chemoradiation (pooled hazard ratio, 0.87; 95% confidence interval, 0.79 to 0.96), increasing survival from 15% to 19% at two years (absolute benefit, 4%) and from 5% to 7% at five years (absolute benefit, 2%). Chemotherapy combinations not including cisplatin did not demonstrate a statistically significant survival benefit.

- Two of seven trials compared radiotherapy alone to radiotherapy combined with low-dose platinum-based chemotherapy used as a radiosensitizer and detected a statistically significant survival advantage for chemoradiation (estimated three-year survival: 16% versus 2%, p=0.009; 10% versus 2%, p=0.00001). Both trials used concurrent daily cisplatin as the radiosensitizer; however, one trial also used split course radiotherapy, which is generally considered less effective than continuous radiotherapy because of the theoretical possibility of tumour repopulation during the rest period.
- Of seven trials that compared conventional radiotherapy alone with chemoradiation, longer survival was generally associated with the combined treatment, although the difference was statistically significant in only one small trial (n=51). Two of four small trials (32-68 patients per treatment arm) that added platinum-based chemotherapy to hyperfractionated or accelerated radiotherapy detected a statistically significant survival advantage for the combination treatment compared with radiotherapy alone (median: 18 versus 8 months, p=0.0027; 22 versus 14 months, p=0.021).
- One meta-analysis also detected a survival benefit for concurrent compared with sequential chemoradiation at two years (n=711; relative risk, 0.86; 95% confidence interval, 0.78-0.95; p=0.003).
- Three randomized trials, one reported in abstract form, comparing sequential to concurrent chemoradiotherapy detected a statistically significant survival advantage for concurrent treatment (median: 16.5 versus 13.3 months, p=0.04; 16.6 versus 12.9 months, p=0.023; 17.0 versus 14.6 months, p=0.046). Three additional trials compared sequential or concurrent chemoradiation with concurrent chemoradiation followed by consolidated chemotherapy or preceded by induction chemotherapy. In the two trials providing a statistical comparison of survival, no significant differences were detected between treatment schedules.
- Of six fully published trials that compared different chemotherapy regimens or schedules within a combined modality treatment approach, three involved older or non-standard chemotherapy regimens combined with split-course radiotherapy, one involved hyperfractionated chemoradiation with or without weekend chemotherapy and detected no statistically significant survival differences between groups, one compared concurrent with sequential chemoradiation involving two different chemotherapy regimens, and one involved three newer platinum-based chemoradiation combinations, but that trial was not designed to compare survival across treatment groups.

POTENTIAL HARMS

Clinical experience suggests that the toxicity resulting from chemotherapy and/or radiotherapy in the treatment of unresected stage III non-small cell lung cancer (NSCLC) is largely confined to neutropenic-related infection, weight loss, and vomiting. Weight loss and serious infections requiring hospitalization are more prevalent with chemoradiation (sequential or concurrent) compared to radiation alone. Patients receiving concurrent combined chemoradiation or radiation alone

are at risk for radiation pneumonitis and esophagitis, and meta-analyses indicate that severe acute esophagitis is more frequently associated with concurrent chemoradiation compared with radiation alone. Toxicities commonly reported in clinical trials include hematologic toxicity and nausea and vomiting, both associated with combined chemoradiation. Symptom control and quality of life were mainly assessed in trials comparing different radiotherapy schedules and doses, with few reporting a statistically significant difference between schedules.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Full dose vinorelbine (25-30 mg/m^2 weekly) should not be used in combination with cisplatin and concurrent radiotherapy because of toxicity concerns. The two trials of concurrent cisplatin-vinorelbine and radiotherapy reviewed in this guideline used a vinorelbine dose of 12.5-15 mg/m^2 generally administered weekly.
- Evidence for the use of induction chemotherapy before concurrent chemoradiation is currently limited; therefore, the Lung Cancer Disease Site Group believe that, where concurrent chemoradiation is used, the two treatment modalities should be *started* at the same time and as early as possible after diagnosis.
- Insufficient evidence exists to recommend for or against the use of chemotherapy as consolidation treatment after chemoradiation. However, based on the limited evidence available, if consolidation chemotherapy is used, two to three cycles could be administered.
- Increased toxicity, particularly esophagitis and hematologic events, is associated with the addition of chemotherapy to radiotherapy. The results of one randomized phase II trial comparing three different cisplatin-based doublets combined with concurrent radiotherapy suggest that these toxicities occur more frequently with gemcitabine-cisplatin compared with paclitaxel-cisplatin or vinorelbine-cisplatin.
- Where single fraction radiation is used for symptom palliation, treatment volume and critical structures in the radiation field, such as the spinal cord, need to be given careful consideration in order to minimize potential toxicities.
- The patient and physician should have a full discussion of the benefits, limitations, and toxicities of therapy.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Okawara G, Mackay JA, Evans WK, Ung YC, Lung Cancer Disease Site Group. Management of unresected stage III non-small cell lung cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Jan. 50 p. [117 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1997 Mar 14 (revised 2006 Jan)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Lung Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The primary authors of this guideline report declared no potential conflicts of interest.

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Management of unresected stage III non-small cell lung cancer: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Jan. Various p. (Practice guideline; no. 7-3). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

The following is available:

- Understanding lung cancer: a guide for patients and their families. Toronto (ON): Cancer Care Ontario (CCO), 2004 Sept. 35 p.

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on January 5, 1999. The information was verified by the guideline developer as of February 22, 1999. This NGC summary was updated by ECRI on December 17, 2001 and most recently on July 21, 2003. The most recent information was verified by the guideline developer as of August 6, 2003. This NGC summary was updated by ECRI Institute on June 5, 2007. The updated information was verified by the guideline developer on June 13, 2007.

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